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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,335	09/28/2001	Jacques Mallet	ST 98036-US-PCT	3243

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,335	MALLET ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2006 and 19 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *28 and 34* is/are allowed.

6)☒ Claim(s) *20-27,29-33,35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to the Papers filed 2 March 2006 and 19 April 2006 in response to the Final Office Action mailed 19 December 2005.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2 March 2006 has been entered.

Claims 20-38 were considered in the 19 December Office Action. Claim 20 was amended in the 2 March Paper. Claims 20-38 are pending and under consideration.

Request for Interview

A letter requesting that the Examiner contact Applicant's representative to arrange an interview was received with the 19 March Paper. On 12 June 2006, the Examiner left a voice mail message with B.J. Sadoff which acknowledged receipt of the interview request and requested that Mr. Sadoff contact the Examiner by telephone to arrange a time to discuss the Application. No response to that voice mail had been received as of the mailing of this Office Action.

Response to Amendment

Claim Rejections - 35 USC § 112

Rejection of claims 20-27 and 29-38 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment of claim 20 such that it no longer requires that the promoter and nucleic acid of interest are not from the same gene.

New Grounds

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 35 and 38 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a composition which comprises cells comprising a vector (i.e., genetically modified cells). The specification provides the following teachings:

> The invention also relates to any composition which comprises cells such as those described above. (p. 25, ¶2);
>
> [T]he invention relates to a method for the regulated expression of nucleic acids in the nervous system, which method comprises implanting a cell, such as defined above, into the nervous system of a patient...(p. 25, ll. 17-22); and
>
> [T]he invention can be used...in humans, in labeling or bioavailability studies or for medical purposes (p. 27, ll. 20-23).

Thus, the specification teaches that the invention relates to any composition that comprises the genetically modified cells and contemplates introducing the cells into humans.

Therefore, absent evidence to the contrary, claims directed to "a composition comprising cells" as recited in claims 35 and 38 can reasonably be construed as covering a composition that is a human being. As the Office views claims that embrace modified human beings as non-statutory subject matter, the claims are properly rejected under 35 USC §101 as directed to non-statutory subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-27, 29 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bujard *et al.* (1997) US Patent No. 5,650,298. This rejection was previously set forth in the Office Action mailed 23 December 2004 and withdrawn when the claims were limited to such that the first promoter and the nucleic acid of interest are not from the same gene. As the claims are now amended such that the distinguishing limitation is no longer recited, Bujard *et al.* again anticipates the claimed invention.

The claims are generally drawn to a tetracycline regulated expression system. More particularly, the claims are drawn to an isolated nucleic acid comprising a first region that encodes a tetracycline operon transactivator, a second region comprises a nucleic acid of interest under control of a tetracycline sensitive promoter, where both regions are arranged in the same

transcriptional orientation, and the transactivator activates expression of the nucleic acid of interest. Further limitations are drawn to a third region placed in between the first and second, where the third region restricts transcriptional interference.

Additional embodiments are directed to the promoter linked to the tTA is a β actin promoter, the protein of interest can be "trophic factors" which is interpreted as broadly as reasonable to mean any protein involved in growth/nutrition.

Bujard *et al.* teaches a tetracycline-regulated expression system inserted into a mammalian genome (e.g. mouse) by means of homologous recombination. (See, e.g., Abstract, Fig. 13A-B, col. 5, ll. 1-25). In particular, Bujard *et al.* teaches, "In a preferred embodiment, integration of the tTA-encoding sequences into a predetermined location in a gene of interest (by homologous recombination) places the tTA-coding sequences under the control of regulatory elements of the gene of interest (e.g., 5' flanking regulatory elements), such that the tTA is expressed in a spatial and temporal manner similar to the gene of interest" (col. 3, ll. 15-21). In the first full paragraph in column 20, Bujard *et al.* describes a targeting vector for use in creating the preferred embodiment as follows (emphasis added):

> In yet another embodiment of the invention, embryonic stem (ES) cell technology can again be used to prevent or promote expression of a gene interest in a conditional manner using a single homologous recombination step that will result in the integrated copy shown in FIG. 13. In this method, a DNA construct containing a fusion of the sequences that normally flank the endogenous gene of interest at the 5' end (**and contain sequences commonly referred to as promoter sequences**) are fused to the DNA sequences encoding the tTA molecule. At the 3' end of the tTA coding sequence, DNA sequences encoding resistance to a selectable marker are typically included. For example, a neomycin resistance gene, which may be fused to either a constitutive regulatory element (e.g., a pPGK promoter as depicted in FIG. 13A) or to a tet operator sequence(s) (as depicted in FIG. 13B) can be inserted at the 3' end of the tTA encoding sequence. When the selectable marker is operably linked to a tet operator sequence(s), its expression is regulated by the tTA (e.g., a resistance phenotype will be expressed in the absence but not the presence of Tc). Finally, 3' of the selectable marker sequences in this DNA

construct are inserted the DNA sequences encoding the endogenous gene of interest, which are also fused to at least one tet operator sequence and a minimal promoter.

As clearly shown in Figure 13, the gene encoding the transactivator and the gene of interest (i.e., either one of the selectable marker resistance gene or the endogenous gene of interest) are arranged in the same transcriptional orientation. The targeting vector thus contemplated by Bujard *et al.* comprises all of the elements of the instant claimed nucleic acid. Alternatively, Bujard *et al.* teaches that the tetracycline-regulated system can be under spatial and temporal control of the β-actin promoter. (E.g. col. 23, l. 2). Furthermore, the construct comprises a third region, which is arranged in between which restricts transcriptional interference, e.g. tTA transactivator. (col. 20, last ¶ bridging to col. 21). In addition, the protein of interest that can be thus regulated can be virtually any desired protein, including growth/nutrition related proteins such as erythropoietin, growth hormone, dystrophin and tyrosine hydroxylase (e.g. col. 28, ll. 50-60).

Thus, Bujard *et al.* teaches an isolated nucleic acid comprising all of the elements of the claimed invention. Therefore, Bujard *et al.* anticipates the rejected claims.

Claims 29-32, 35 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu *et al.* (August 1997) *Cancer Res.* 57:3339-3343 (previously made of record).

The claims are directed to a vector "which comprises a nucleic acid according to claims 20 or 28", cells comprising the vector and a composition comprising the cells comprising the vector. In some claims, the cell is limited to a mammalian cell and the vector is limited to being an adenoviral vector.

Because the base claim (claim 29) refers to the nucleic acid comprised in the vector using an indefinite article (i.e., "a nucleic acid according to claims 20 or 28") rather than a definite article (i.e., "the nucleic acid according to claims 20 or 28") the claims are reasonably construed as encompassing a vector comprising any nucleic acid of the cited claims. For example, the vector of the claims is reasonably construed as embracing a vector comprising "a nucleic acid which encodes the transactivator of the tetracycline-regulated system" as recited in claim 20. Therefore, the adenovirus vector illustrated in Figure 1 of Hu *et al.*, which comprises a nucleic acid which encodes the transactivator of the tetracycline-regulated system anticipates the vector of the instant claims. Likewise, the mammalian cells transduced with the vector and compositions comprising the transduced cells anticipate the cells and compositions of the instant claims (see, e.g., the section entitled "Efficient, Tc-regulated Production of Recombinant Human TNF-α in Various AdVtTA.TNF-α-transduced Human and Mouse Cells" commencing on page 3341).

Thus, Hu *et al.* teaches vectors and cells comprising all of the elements of the claimed invention. Therefore, Hu *et al.* anticipates the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-27, 29, 31-33 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (Supra), further in view of Corti et al. *NeuroReport*, 1996; 7:1655-1659 (previously made of record).

The claims are interpreted consonant with the interpretations set forth in discussion of the rejection under the 35 U.S.C. 102. Additional embodiments, are drawn to the transcription terminator being an upstream mouse sequence (UMS), that 1-10 sequences of the tet-responsive (tetOP) elements are present in the second promoter which is a minimal CMV promoter and that an isolated nerve cell can contain the claimed nucleic acid molecule borne in a recombinant adenovirus.

Bujard *et al.* also teaches that the second promoter can be a CMV minimal promoter (i.e. without enhancer elements) that contain up to seven tetOP elements. (e.g. col. 5, ll. 60-66; col. 6, ll. 55-65).

Bujard *et al.*, although indicating any human cell can be any mammalian cell, does not expressly indicate nerve cell, nor does the '298 patent indicate that the tet-expression system

taught, can be incorporated in an adenoviral vector. Furthermore, the '298 patent doesn't specifically indicate that the transcription terminator can be a UMS, but does indicate that any suitable transcription terminator (affecting the tet-regulated expression) as known in the art can be used. (e.g. col. 21, ¶ 1).

Corti et al. generally teaches a tet-expression system (tTA system) in nerve cells. More particularly, Corti et al. teach a construct that comprises the tTA system under control of a CMV promoter as well as a reporter gene under a minimal CMV promoter with the two transcription units being separated by a UMS sequence, all oriented in the same direction. Corti et al. teach a tetracycline regulatory system for the regulation of genes introduced into the CNS. (e.g. p. 1658, col. 2, last ¶).

Therefore, it would have been obvious for one of skill to use the UMS transcription terminator in the tetracycline-expression system as taught by Bujard *et al.* One of skill would have been motivated to make this minor modification by virtue of the express statement in Bujard *et al.* that other transcription terminators can be used and the teaching of Corti et al. that the UMS transcription terminator was well known at the time of invention. Therefore, the artisan would have been motivated to use transcription terminators, such as UMS, to expand the range of terminators to be used in the tTA-regulated system. Given the skill and knowledge at the time of invention, there would have been a reasonable expectation of success to use the UMS as one of many transcription terminators in the tTA-regulated system.

In addition, Corti et al. indicate that the vector-borne tTA system can be used in nerve cells. Bujard *et al.* indicates that the tTA system taught therein can be used in any mammalian cell. Either the '298 patent or Corti et al. teach a vector-borne tTA system, with the only

variation in the constructs being that Corti et al. teaches the first promoter being a viral CMV promoter. However, this variation is also explicitly taught in Bujard *et al.* (e.g. col. 22, last ¶ bridging to col. 23; indicating that the first promoter can be a constitutive promoter such as CMV, as is also taught by Corti et al.). Therefore, it would have been obvious to use the Bujard *et al.* vector-borne tTA system in nerve cells. One of skill would have been motivated to do such, so as to broaden the scope of potential cells in which the tTA system can be used to regulate gene expression. Given the skill and knowledge at the time of invention, there would have been a reasonable expectation of success to utilize a tTA system as taught by the '298 patent in nerve cells.

Allowable Subject Matter

Claims 28 and 34 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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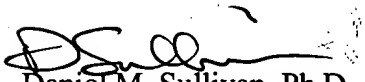

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